Catalytic Enantioselective Dihalogenation and the Selective Synthesis of (−)-Deschloromytilipin A and (−)-Danicalipin A

Matthew L. Landry, Dennis X. Hu, Grace M. McKenna, and Noah Z. Burns*

**Stereoselective dihalogenation of alkenes**

\[
\text{Ar} \text{CH}_2 \text{OH} \xrightarrow{(\text{DHQ})_2\text{PHAL} (20 \text{ mol\%})} \xrightarrow{\text{ArCl}_2 (2.0 \text{ eq})} \xrightarrow{\text{CH}_2\text{Cl}_2, -78 \degree \text{C to r.t.}} \text{Cl} \xrightarrow{\text{Yield: 32–81 \%}} \xrightarrow{\text{ee: 25–81 \%}} \text{Cl}
\]


\[
\text{HO} \xrightarrow{\text{PhSeSePh (5 mol\%)} \xrightarrow{\text{BnEt}_3\text{NCl (3.0 eq)}} \xrightarrow{[\text{PyF}^+][\text{BF}_4^-] (1.3 \text{ eq})} \xrightarrow{\text{TMSCl (2.0 eq)}} \xrightarrow{\text{MeCN, r.t.}} \text{Cl} \xrightarrow{\text{Yield: 37–71 \%}} \xrightarrow{\text{ee: 80–91 \%}} \text{Cl}
\]


\[
\text{HO} \xrightarrow{\text{NBS (1.05 eq)}} \xrightarrow{\text{CITi(Oi-Pr)}_3 (1.1 \text{ eq})} \xrightarrow{\text{10–30 mol\% (S,R)-D hexanes, -20 \degree \text{C}} \xrightarrow{\text{Yield: 56–94 \%}} \xrightarrow{\text{ee: 78–97 \%}} \text{Cl}
\]


**This work**

\[
\text{HO} \xrightarrow{\text{t-BuOCl (1.1 eq)}} \xrightarrow{\text{CITi(Oi-Pr)}_3 (1.1 \text{ eq})} \xrightarrow{\text{10–30 mol\% (S,R)-D hexanes, -20 \degree \text{C}} \xrightarrow{\text{Yield: 45–94 \%}} \xrightarrow{\text{ee: 80–86 \%}} \text{Cl}
\]

Chlorosulfolipids (CSLs)

- Isolation: *Ochromonas danica* and *Poterioochromonas malhamensis* in 1962

Research on CSLs are difficult owing to the lack of availability of CSLs from natural resources and chemical access to CSLs.
A challenge in Enantioselective Dichlorination

**Problem 1:** Selective formation of chloronium ion

**Problem 2:** Regiochemical control in chloride delivery

= regioisomeric dichlorides are enantiomers
Development of an Enantioselective Dechlorination

![Chemical structures and reactions]

<table>
<thead>
<tr>
<th>entry</th>
<th>$X^+$ source</th>
<th>conditions</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS</td>
<td>30 mol% 11, hexanes, r.t.</td>
<td>90</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>NBS</td>
<td>30 mol% 11, hexanes, -20 °C</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>NCS</td>
<td>30 mol% 11, hexanes, r.t.</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>30 mol% 11, hexanes, r.t.</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>PhICl$_2$</td>
<td>30 mol% 11, hexanes, r.t.</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>30 mol% 11, hexanes, r.t.</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>30 mol% 11, hexanes, r.t.</td>
<td>66</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>t-BuOCl</td>
<td>30 mol% 11, hexanes, r.t.</td>
<td>56</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>t-BuOCl</td>
<td>30 mol% 12, hexanes, r.t.</td>
<td>73</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>t-BuOCl</td>
<td>30 mol% 11, CH$_2$Cl$_2$, r.t.</td>
<td>62</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>t-BuOCl</td>
<td>30 mol% 11, Et$_2$O, r.t.</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>12</td>
<td>t-BuOCl</td>
<td>30 mol% 11, hexanes, -20 °C</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>13</td>
<td>t-BuOCl</td>
<td>10 mol% 11, hexanes, -20 °C</td>
<td>82</td>
<td>76</td>
</tr>
</tbody>
</table>

a) Ratio of bromochloride constitutional isomers.
Proposed Mechanism

\[ \text{Cl}^{+} \text{ source} \]
\[ \text{ClTi(Oi-Pr)}_3 \]
\[ 30 \text{ mol\% 11} \]

hexanes, r.t.

\[ \text{Proposed intermediate} \]

\[ \text{Cl}^{+} = \text{NCS: 62\% ee (52\% yield)} \]

\[ \text{Cl}^{+} = \text{tBuOCl: 72\% ee (56\% yield)} \]
# Dichlorination Substrate Scope

![Chemical structure of substrate and product](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield (%)</th>
<th>ee (%)</th>
<th>mol (%) 11</th>
<th>product</th>
<th>prior art or use in synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(-)OH 16</td>
<td>83</td>
<td>91</td>
<td>10</td>
<td>(+)-17</td>
<td>Nicolaou (2011): 58%, 61% ee ArCl₂, 20 mol% (DHQD)_2PHAL</td>
</tr>
<tr>
<td>2</td>
<td>Me(-)OH 18</td>
<td>64</td>
<td>80</td>
<td>15</td>
<td>(+)-19</td>
<td>(dechloro)mytilipin A Vanderwal (2013): (R)-19 Burns (this work): (+)-19</td>
</tr>
</tbody>
</table>
| 3     | Me\(-\)OH 4\(\)OH 20 | 86        | 83     | 15         | (−)-21  | danicalipin A
|       | Me\(-\)OH 6\(\)OH 22 | 64        | 81     | 20         | (+)-23  | malhamensilipin A Vanderwal (2014): (R)-23 |
| 4     | Me\(-\)OH 24 | 45        | 85     | 30         | (+)-25  | nominal undecachlorosulfolipid (yet to be utilized) |
| 5     | Ph\(-\)OH 26 | 61        | 90     | 30         | (+)-27  | Burns (2015) |
# Dibromination Substrate Scope

\[
\text{NBS, BrTi(Oi-Pr)_3} \quad \text{a)}
\]

15–20 mol % (R,S)-11 hexanes, -20 °C

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield (%)</th>
<th>ee (%)</th>
<th>mol (%) 11</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 b)</td>
<td>Ph-[\text{16}]OH</td>
<td>75</td>
<td>87</td>
<td>15</td>
<td>(+)-28</td>
</tr>
<tr>
<td>2</td>
<td>Me-[\text{18}]OH</td>
<td>82</td>
<td>80</td>
<td>20</td>
<td>(+)-29</td>
</tr>
<tr>
<td>3 c)</td>
<td>Me-[\text{20}]OH</td>
<td>86</td>
<td>80</td>
<td>15</td>
<td>(-)-30</td>
</tr>
<tr>
<td>4 c)</td>
<td>Me-[\text{22}]OH</td>
<td>79</td>
<td>86</td>
<td>20</td>
<td>(+)-31</td>
</tr>
<tr>
<td>5 c)</td>
<td>Ph-[\text{26}]OH</td>
<td>84</td>
<td>81</td>
<td>20</td>
<td>(+)-27</td>
</tr>
</tbody>
</table>

a) Conditions unless otherwise noted: 1.1–1.2 equiv NBS, 1.1–1.3 equiv BrTi(Oi-Pr)_3, 15–20 mol % (R,S)-11, hexanes, -20 °C, 4–12 h. b) 3:1 hexanes/CCl₄. c) absolute configuration unconfirmed.
Synthesis of (−)-Deschloromymytilipin A

1. DMP (1.3 eq) NaHCO₃ (3.0 eq) CH₂Cl₂, 0 °C
   - 33 (1.0 eq) n-BuLi (1.2 eq) TFAA (1.3 eq) THF, -78 °C
   - MeCl OH

2. 1) acryloyl chloride (2.0 eq) DIPEA (1.8 eq) DMAP (0.2 eq) CH₂Cl₂, 0 °C, 80%
   - 2) HG-II (2 mol%) toluene, 90 °C 86%
   - 35

3. NaBH₄ (2.4 eq) CeCl₃·H₂O (2.4 eq)
   - EtOH, r.t., 97%
   - 36

4. Tf₂O (1.2 eq) 2,6-lutidine (1.2 eq) CH₂Cl₂, 0 °C, 82 %
   - TES OTf (1.7 eq) 2,6-di-tert-butylpyridine (1.7 eq) CH₂Cl₂, 0 °C, 85 %
   - 38

5. CuCl (0.1 eq) TMEDA (0.3 eq) A (1.2 eq)
   - THF, 0 °C to r.t., then 1M eq. HCl MeOH, rt, 28 %
   - 38'

6. SO₃·Pyridine (3.0 eq)
   - THF, r.t., 94 %
   - (-)-Deschloromymytilipin A
**Synthesis of Stereotetrad**

1. **Step 1**
   - Compound: (-)-29
   - Reagents: DMP (1.3 eq), NaHCO₃ (3.0 eq)
   - Conditions: CH₂Cl₂, 0 ºC
   - Product: 39
   - Yields: THF, -78 ºC, 57%

2. **Step 2**
   - Compound: 39
   - Reagents: n-BuLi (2.1 eq), allyl bromide (2.1 eq), AlEt₂Cl (4.0 eq)
   - Conditions: THF, -78 ºC
   - Product: 41

3. **Step 3**
   - Compound: 41
   - Reagents: acryloyl chloride (1.5 eq), DIPEA (1.0 eq), DMAP (0.2 eq)
   - Conditions: CH₂Cl₂, 0 ºC
   - Product: 42
   - Yields: 61%

4. **Step 4**
   - Compound: 42
   - Reagents: HG II (2.5 mol%), toluene, 90 ºC
   - Conditions: EtOH, 0 ºC
   - Product: 43
   - Yields: 82%
1. Synthesis and characterization of polybromide stereohexads would help confirm the existence of putative bromosulfolipids.

2. Conformational data on stereohexads could provide insight into the manner in which these molecules assemble in a lipid membrane.

3. Investigation of unnatural stereohexads would expand the repertoire of characterization data for complex polyhalostereoarrays.
Concise Synthesis of (−)-Danicalipin A

1) ICl (2.0 eq)
2,6-lutidine (3.0 eq)
CH₂Cl₂, 0 °C to r.t., 74%

2) 55 (1.1 eq)
aq. NaOH
THF, 0 °C, 85%

CH₂Cl₂ (1.5 eq)
n-BuLi (1.1 eq)
THF, -100 °C
then
ZnCl₂ (1.0 eq)
-100 °C to r.t.
(ref. 1)

59 (1.0 eq)
t-BuLi (1.1 eq)
Et₂O/Hexanes, -78 °C;
MgBr₂·Et₂O (1.2 eq)
then
57 (1.1 eq), THF
-78 °C to r.t.
24% from 56

59 (1.0 eq)
t-BuLi (1.1 eq)
Et₂O/Hexanes, -78 °C;
MgBr₂·Et₂O (1.2 eq)
then
57 (1.1 eq), THF
-78 °C to r.t.
24% from 56

1) CD₂OD, r.t.;
concentrate;
Me₄N(Cl₂Br) (1.1 eq)
CH₃CN, r.t.

2) Bu₃SnH (1.1 eq)
Et₃B (0.2 eq)
air, toluene, -78 °C
3) ClSO₃H, CH₂Cl₂, rt
21 % overall

Reference
Rationale for the Effect of O-Deuteration